*Clinical Investigation*

# The Role of Interleukin-6 in Cases of Cardiac Myxoma

## Clinical Features, Immunologic Abnormalities, and a Possible Role in Recurrence

**Cesar Emilio Mendoza, MD**
**Manuel Francisco Rosado, MD**
**Leon Bernal, MD**

*We performed this prospective study to evaluate the correlation of interleukin-6 serum levels with preoperative constitutional symptoms and immunologic abnormalities, and the possible role played by this cytokine in tumor recurrence.*

*Eight patients with atrial myxoma were evaluated at our institution from July 1993 to November 1998. We measured their interleukin-6 serum levels by enzyme-linked immunosorbent assay method preoperatively and 1 and 6 months after surgery. Two of the cases involved recurrent tumor; 1 patient had undergone his 1st surgery at a different institution and died during the 2nd procedure, so his data were incomplete.*

*Preoperatively, the whole group of patients had elevated interleukin-6 serum levels. Although patients with a 1st occurrence of tumor demonstrated a positive correlation between interleukin-6 serum level and tumor size, the 2 patients with recurrent tumors appeared to have higher interleukin-6 levels regardless of tumor size. Once the tumor was surgically removed, interleukin-6 levels returned to normal values, and this was associated with regression of clinical manifestations and immunologic features.*

*According to our study, the overproduction of interleukin-6 by cardiac myxomas is responsible for the constitutional symptoms and immunologic abnormalities observed in patients with such tumors and might also play a role as a marker of recurrence. This study also suggests that recurrent cardiac myxomas form a subgroup of cardiac myxomas with a highly intrinsic aggressiveness, as implied by their greater interleukin-6 production despite their smaller size. Further studies are needed to confirm these results.* ***(Tex Heart Inst J 2001;28:3-7)***

***Key words:*** *Constitutional symptoms; heart atrium; heart neoplasms; immunologic abnormalities; interleukin-6; myocardium/pathology; myxoma; neoplasms, second primary; tumor markers, biological*

***From:*** *Division of Cardiology (Dr. Mendoza) and Division of Clinical Oncology (Dr. Rosado), Peruvian National Heart Institute, Guillermo Almenara Hospital, Lima, Peru; and Internal Medicine Department (Dr. Bernal), Jackson Memorial Hospital, Miami, Florida 33136-1094*

***Address for reprints:*** *Cesar Emilio Mendoza, MD, Internal Medicine Department, Jackson Memorial Hospital, 1611 NW 12th Avenue, Miami, FL 33136-1094*



Cardiac myxomas are the most common primary tumor of the heart. In a study of the surgical incidence of atrial myxoma during a 15-year period,[1] the incidence in the Republic of Ireland was 0.5 atrial myxomas per million admissions to the National Cardiac Surgery Unit per annum. Although the neoplastic nature of cardiac myxomas was previously questioned[2] and the histogenesis of these tumors is still not completely clear, most studies support the position that cardiac myxomas are true neoplasms arising from primitive multipotential mesenchymal cells.[3-6] Since the initial report of Hirano and colleagues,[7] many other studies have confirmed that cardiac myxomas produce interleukin-6 (IL-6) constitutively, which is a possible explanation for the inflammatory and immune features observed in patients with this tumor.[8-15] Interleukin-6 is a multifactorial cytokine that produces differentiation and proliferation of normal and malignant cells,[16] induction of the acute-phase response,[17] and fever. It also mediates the induction of intercellular adhesion molecule 1 (ICAM-1).[18] The aim of the present study was to correlate IL-6 serum levels with preoperative constitutional symptoms, immunologic abnormalities, and postoperative tumor recurrence.

## Patients and Methods

Between July 1993 and November 1998, 8 consecutive patients with nonfamilial myxoma were evaluated and surgically treated at our institution. Six patients were female and 2 were male; the ages ranged from 15 to 64 years (mean, 36 yr). Two patients, 1 male and 1 female, had undergone previous surgery for cardiac myxoma and now presented with recurrent tumors. One of these patients (the male) has been excluded from much of the following report, because he died intraoperatively

and his results are incomplete. See Table I for clinical features of the 7 survivors.

All patients were extensively interviewed and examined. Two-dimensional transthoracic and transesophageal echocardiography were used to determine the location and size of the tumor, the site of pedicle attachment, and the presence of tumor prolapse. Surgical excision of the tumor was performed as soon as possible after diagnosis. The surgical approach was biatrial and the tumor was excised together with a cuff of endocardium around its point of attachment. A pathologist confirmed each diagnosis.

### Laboratory Tests

In addition to the routine clinical tests, we performed in each patient the following laboratory studies before surgery, and again at 1 and 6 postoperative months: IL-6 serum levels, erythrocyte sedimentation rate, C-reactive protein levels, serum protein electrophoresis, quantification of serum immunoglobulins (IgG, IgA, and IgM), and tests for the detection of serum rheumatoid factor and antinuclear antibodies.

*Immunologic Abnormality.* Patients were classified as having an immunologic abnormality if they exhibited at least 2 of the following findings: erythrocyte sedimentation rate >25 mm/hr, C-reactive protein >0.8 mg/dL, a gamma globulin serum level >20%, the presence of an abnormal immunoglobulin level, a positive rheumatoid factor (>20 IU), and the presence of antinuclear antibodies.

*IL-6 Measurements.* A 10-mL sample of blood was obtained by venipuncture from all patients pre- and postoperatively. Each sample was collected into tubes containing ethylenediaminetetracetic acid and was centrifuged immediately at 4 °C. Plasma was stored at −80 °C until an assay of IL-6 was achieved. The plasma concentration of IL-6 was determined by an enzyme-linked immunosorbent assay method (ELISA) (R&D Systems; Minneapolis, Minn), using mouse antihuman IL-6 monoclonal antibody. As controls for the ELISA method, we used IL-6 measurements from the serum of 5 healthy donors.

### Follow-Up

Follow-up of all 7 survivors was performed during the first 6 postoperative months by means of clinical examination and 2-dimensional echocardiographic studies. At 1 and 6 postoperative months, as mentioned above, we also repeated the preoperative laboratory tests and compared early and late results. Additional follow-up was performed on patient 3 at 6-month intervals, until she presented with recurrence of the tumor.

## Results

*Clinical Features and Immunologic Abnormalities.* The preoperative clinical features, immunologic abnormalities, and IL-6 serum levels of the 7 surviving patients with primary cardiac myxomas are summa-

**TABLE I.** Preoperative Clinical Features, Immunologic Abnormalities, and Interleukin-6 Serum Levels in 7 Surviving Patients with Primary Cardiac Myxoma

| | Surviving Patients | | | | | | |
|---|---|---|---|---|---|---|---|
| | **1** | **2** | **3*** | **4** | **5** | **6** | **7** |
| **Clinical features** | | | | | | | |
| Age (years), sex | 42F | 27F | 15F | 29F | 38M | 45F | 64F |
| Constitutional symptoms | + | + | + | − | − | − | + |
| Obstruction of blood flow | − | + | + | − | + | + | + |
| Asymptomatic | − | − | − | + | − | − | − |
| Hemoglobin (g/dL) | 10.5 | 11.0 | 12.1 | 11.9 | 13.8 | 11.9 | 12.0 |
| **Immunologic markers** | | | | | | | |
| ESR (mm/hr) | 64 | 59 | 67 | 23 | 27 | 20 | 34 |
| C-reactive protein (mg/dL) | 12.7 | 8.5 | 7.5 | 0.9 | 1.1 | 1.0 | 4.4 |
| Gamma globulin (%) | 22 | 24 | 22.6 | 20.5 | 19.6 | 19.9 | 20 |
| Rheumatoid factor | + | + | + | − | − | − | − |
| Antinuclear antibodies | − | + | − | − | − | − | − |
| **Other data** | | | | | | | |
| Interleukin-6 (pg/mL) | 40 | 46.2 | 39 | 5.6 | 6.1 | 5.3 | 9.3 |
| Site of tumor | LA | LA | RA | LA | LA | MV | LA |
| Size of tumor (mm) | 81×78×65 | 100×95×90 | 63×62×60 | 28×27×25 | 34×32×3 | 28×28×16 | 55×52×50 |
| Tumor size index ($cm^3$) | 410 | 855 | 234 | 19 | 33 | 13 | 143 |

ESR = erythrocyte sedimentation rate; F = female; LA = left atrium; M = male; MV = mitral valve; RA = right atrium

*This patient presented with recurrence.

rized in Table I. Constitutional symptoms present in 4 of these patients included fever, malaise, weight loss, myalgias, and arthralgias. Five patients had symptoms associated with obstruction of the intracardiac blood flow, and 1 patient was asymptomatic at the time of the diagnosis. Five patients showed immunologic abnormalities, 3 of them with clinical manifestations. Myxomas were present in the left atrium in 6 patients and in the right atrium in 1 patient. Tumor size ranged from 28 × 28 × 16 mm to 100 × 95 × 90 mm. Macroscopically, the lesion was pedunculated and papillary in 5 patients, and it was sessile, smooth, and polypoid in 2 patients. Light microscopic examination showed the typical features of cardiac myxomas in the whole group of patients.

*IL-6 Serum Levels*. Compared with the mean IL-6 serum level of 5 healthy controls (3.6 pg/mL), the whole group of surviving patients (n=7) had elevated IL-6 serum levels (Table I) at the time of their initial diagnosis (mean, 21.6 pg/mL; range, 5.3 to 46.2 pg/mL). Six of these 7 patients with increased levels of IL-6 had immunologic abnormalities; 4 had a wide range of constitutional symptoms. Importantly, there was a significant correlation between patients' IL-6 serum levels and the presence and intensity of constitutional symptoms: patients with higher IL-6 levels experienced more intense and diverse systemic manifestations. In this study, the threshold of IL-6 serum level for the development of asymptomatic immunologic abnormalities seemed to be 5.6 pg/mL, while the threshold for the appearance of constitutional symptoms seemed to be 9.3 pg/mL. Table II shows the progressive lowering of IL-6 serum levels during the first 6 months after surgical excision of the myxomas. This reduction was accompanied by a marked regression of immunologic and clinical features by the 1st postoperative month and by the complete resolution of the preoperative abnormalities by the 6th month after surgery.

*IL-6 Serum Levels in Relation to Tumor Size*. Using the tumor-size index described by Soeparwata and associates,[14] we found a positive correlation of this index to the IL-6 serum levels in our patients with 1st-time myxomas: the greater the tumor-size index, the higher the IL-6 serum level and the more intense the constitutional symptoms. The threshold of tumor-size index for the development of asymptomatic immunologic abnormalities appeared to be 19 $cm^3$, and the threshold for constitutional symptoms appeared to be 143 $cm^3$.

*IL-6 Serum Levels, Immunologic Abnormalities, and Constitutional Symptoms in Relation to Tumor Recurrence*. Two patients presented with tumors that had recurred within a 27-month mean postoperative period after excision of previous cardiac myxomas (Table III). Patient 3 presented with a recurrent tumor attached to the left atrial posterior wall. Patient 8 showed 2 tumors located in the left atrium, 1 arising from the interatrial septum and the other from the posterior wall of the left atrium. All tumors showed pathologic features consistent with those of a benign cardiac myxoma. Both patients had strongly increased IL-6 serum levels, together with an ample array of immunologic abnormalities and constitutional symptoms. Patient 8 had undergone his 1st surgery at another center, so we lack the pertinent laboratory information concerning his 1st tumor. This patient displayed the highest IL-6 serum level (102 pg/mL) found in our study group, accompanied by marked immunologic and constitutional manifes-

**TABLE II.** Primary Cardiac Myxomas: Interleukin-6 Serum Levels Preoperatively and Postoperatively among the 7 Operative Survivors

| | **Interleukin-6** (pg/mL) | | |
|---|---|---|---|
| **Patient No.** | **Preoperatively** | **1 Month** | **6 Months** |
| 1 | 40.0 | 6.4 | 2.2 |
| 2 | 46.2 | 5.0 | 2.1 |
| 3 | 39.0 | 6.0 | 1.8 |
| 4 | 5.6 | 1.1 | 1.2 |
| 5 | 6.1 | 3.0 | 2.9 |
| 6 | 5.3 | 4.7 | 4.2 |
| 7 | 9.3 | 4.2 | 3.9 |

**TABLE III.** Interleukin-6 Serum Levels in Patients with Recurrent (2nd Primary) Tumors

| | **Patients** | |
|---|---|---|
| | **3** | **8*** |
| **Clinical features** | | |
| Age (years) at primary tumor, sex | 15F | 26M |
| Constitutional symptoms | – | + |
| Obstruction of blood flow | – | – |
| **Immunologic markers** | | |
| ESR (mm/hr) | 90 | 77 |
| C-reactive protein (mg/dL) | 12.7 | 13 |
| Gamma globulin (%) | 25.2 | 26 |
| Immunoglobulin (mg/dL) | 1970 (IgG) | 2211 (IgG) |
| Rheumatoid factor | + | + |
| Antinuclear antibodies | – | NM |
| **Other data** | | |
| Interleukin-6 (pg/mL) | 77 | 102 |
| Site of 1st myxoma | RA | LA |
| Time of recurrence (years) | 3 | 1.5 |
| Site of recurrent tumor | LA | LA |
| Size of recurrent tumor (mm) | 36×31×38 | 42×40×36 (IAS)<br>21×18×17 (PW) |
| Tumor size index | 42 | 66** |

ESR = erythrocyte sedimentation rate; F = female; IAS = interatrial septum; LA = left atrium; M = male; NM = not measured; PW = posterior wall; RA = right atrium

*This patient died at time of surgery.
**This is the sum of both tumor-size indices.

tations. Patient 3 showed a similar clinical and serologic pattern; however, her recurrent features were markedly more prominent than those associated with her 1st tumor. Patient 8 presented with a total tumor size of 66 $cm^3$ (the sum of both tumor-size indices); patient 3 had only a single tumor with a size index of 42 $cm^3$. When comparing the indices of patients in this small recurrent-tumor cohort with those observed in the nonrecurrent-tumor cohort, we could not demonstrate the previously observed positive correlation between IL-6 serum levels and tumor size.

## Discussion

Shortly after Hirano's group[7] demonstrated that cardiac myxomas produce IL-6, subsequent studies showed that the overproduction of this cytokine is responsible for the constitutional symptoms and immunologic features observed in myxoma patients.[8-15] Interleukin-6 is a pleiotropic cytokine with 4 properties that are relevant herein. It is a potent B cell differentiation factor, which induces the synthesis of polyclonal immunoglobulins; it is a strong hepatocyte-stimulating factor, which induces the release of acute-phase proteins; it is a potent cell-proliferative factor; and finally, it is an inducer of ICAM 1, a factor implicated in the mechanism of cellular adhesion.[12,16-18]

This study corroborates previous observations that constitutional symptoms and immunologic abnormalities of cardiac myxomas are due to the production of IL-6. This is supported by the postoperative regression of clinical and immunologic features that accompanies normalization of IL-6 serum levels. Interestingly, all cardiac myxomas were associated with elevated IL-6 levels, independently of the presence of immunologic features and constitutional symptoms. According to our results, it seems that immunologic abnormalities and constitutional symptoms appear only after IL-6 serum levels exceed a certain threshold, as suggested by Soeparwata and colleagues.[14] In addition, our results support the observation that the size of the tumor directly correlates with the amount of circulating IL-6, the development of constitutional symptoms, and immunologic abnormalities.[14] Of considerable interest is the fact that IL-6 cannot only stimulate B cell proliferation and differentiation but can promote the growth of plasmocytomas, myelomas, T and B cell lymphomas, and Kaposi's sarcoma, sometimes in an autocrine manner.[19-21] Although it has not been shown that cardiac myxomas can enlarge by IL-6 autocrine stimulation, this is a possibility that merits further study.

Our limited data suggest that recurrent cardiac myxomas may have a different biological behavior, as evidenced by the fact that these tumors appear to produce higher IL-6 serum levels without regard to the size of the tumor. This could indicate a more aggressive pattern, despite histologic proof that the tumor is benign.

The mechanism responsible for tumor recurrence remains unclear. The debate is focused upon intracardiac seeding via detached tumor fragments carried by the bloodstream, local recurrence due to inadequate resection or malignant transformation, and the presence of multifocal disease. Although a recent report[22] suggests that multifocal disease is the most likely explanation for the recurrence of cardiac myxomas, the possibility of a progressive change in the biologic nature of the tumor cannot be excluded, especially in cases of local recurrence. At least 1 of our 2 patients with tumor recurrence showed very high levels of IL-6 at the time that her 1st tumor was diagnosed and displayed local recurrence despite an appropriate surgical resection. This, together with the evidence that IL-6 mediates the induction of ICAM 1, raises the possibility that a cardiac myxoma that produces high levels of this cytokine might have a higher rate of recurrence. In cases of multifocal recurrence, IL-6 might also play a role, in which it induces the activation and proliferation of secondary foci. The answer to such questions may be obtained through further studies.

## Conclusion

Our findings confirm that the overproduction of IL-6 by cardiac myxomas is responsible for the immunologic abnormalities and constitutional symptoms seen in patients with such tumors, corroborates the significant correlation between IL-6 serum levels and primary tumor size, and suggests that IL-6 might play an important role in recurrence and might therefore have clinical use as a tumoral marker and recurrence indicator. Finally, it is interesting to speculate on the possibility that recurrent tumors are a subgroup of cardiac myxomas with a highly intrinsic aggressiveness as reflected by their greater IL-6 production in relation to their comparatively smaller size.

## References


1. MacGowan SW, Sidhu P, Aherne T, Luke D, Wood AE, Neligan MC, McGovern E. Atrial myxoma: national incidence, diagnosis and surgical management. Ir J Med Sci 1993;162:223-6.
2. Salyer WR, Page DL, Hutchins GM. The development of cardiac myxomas and papillary endocardial lesions from mural thrombus. Am Heart J 1975;89:4-17.
3. Ferrans VJ, Roberts WC. Structural features of cardiac myxomas. Histology, histochemistry, and electron microscopy. Hum Pathol 1973;4:111-46.
4. Bashey RI, Nochumson S. Cardiac myxoma. Biochemical analyses and evidence for its neoplastic nature. N Y State J Med 1979;79:29-32.

5. Dewald GW, Dahl RJ, Spurbeck JL, Carney JA, Gordon H. Chromosomally abnormal clones and nonrandom telomeric translocations in cardiac myxomas. Mayo Clin Proc 1987; 62:558-67.
6. Seidman JD, Berman JJ, Hitchcock CL, Becker RL Jr, Mergner W, Moore GW, et al. DNA analysis of cardiac myxomas: flow cytometry and image analysis. Hum Pathol 1991;22:494-500.
7. Hirano T, Taga T, Yasukawa K, Nakajima K, Nakano N, Takatsuki F, et al. Human B-cell differentiation factor defined by an anti-peptide antibody and its possible role in autoantibody production. Proc Natl Acad Sci U S A 1987;84: 228-31.
8. Jourdan M, Bataille R, Seguin J, Zhang XG, Chaptal PA, Klein B. Constitutive production of interleukin-6 and immunologic features in cardiac myxomas. Arthritis Rheum 1990;33:398-402.
9. Saji T, Yanagawa E, Matsuura H, Yamamoto S, Ishikita T, Matsuo N, et al. Increased serum interleukin-6 in cardiac myxoma. Am Heart J 1991;122:579-80.
10. Wiedermann CJ, Reinisch N, Fischer-Colbrie R, Vollmar AM, Herold M, Knapp E. Proinflammatory cytokines in cardiac myxomas. J Intern Med 1992;232:263-5.
11. Seino Y, Ikeda U, Shimada K. Increased expression of interleukin 6 mRNA in cardiac myxomas. Br Heart J 1993;69: 565-7.
12. Sakamoto H, Sakamaki T, Wada A, Nakajima T, Kanda T, Murata K. Dexamethasone inhibits production of interleukin-6 by cultured cardiac myxoma cells. Am Heart J 1994; 127:704-5.
13. Kanda T, Sakamaki T, Murata K. A cardiac myxoma with interleukin-6 production and cerebral metastasis. Int J Cardiol 1994;45:144-6.
14. Soeparwata R, Poeml P, Schmid C, Neuhof H, Scheld HH. Interleukin-6 plasma levels and tumor size in cardiac myxoma. J Thorac Cardiovasc Surg 1996;112:1675-7.
15. Parissis JT, Mentzikof D, Georgopoulu M, Gikopoulos M, Kanapitsas A, Merkouris K, Kefalas C. Correlation of interleukin-6 gene expression to immunologic features in patients with cardiac myxomas. J Interferon Cytokine Res 1996;16: 589-93.
16. Borden EC, Chin P. Interleukin-6: a cytokine with potential diagnostic and therapeutic roles. J Lab Clin Med 1994; 123:824-9.
17. Castell JV, Gomez-Lechon MJ, David M, Fabra R, Trullenque R, Heinrich PC. Acute-phase response of human hepatocytes: regulation of acute-phase protein synthesis by interleukin-6. Hepatology 1990;12:1179-86.
18. Youker K, Smith CW, Anderson DC, Miller D, Michael LH, Rossen RD, Entman ML. Neutrophil adherence to isolated adult cardiac myocytes. Induction by cardiac lymph collected during ischemia and reperfusion. J Clin Invest 1992;89:602-9.
19. Kawano M, Hirano T, Matsuda T, Taga T, Horii Y, Iwato K, et al. Autocrine generation and requirement of BSF-2/IL-6 for human multiple myelomas. Nature 1988;332:83-5.
20. Tosato G, Tanner J, Jones KD, Revel M, Pike SE. Identification of interleukin-6 as an autocrine growth factor for Epstein-Barr virus-immortalized B cells. J Virol 1990;64: 3033-41.
21. Miles SA, Rezai AR, Salazar-Gonzales JF, Vander Meyden M, Stevens RH, Logan DM, et al. AIDS Kaposi sarcoma-derived cells produce and respond to interleukin 6. Proc Natl Acad Sci U S A 1990;87:4068-72.
22. Shinfeld A, Katsumata T, Westaby S. Recurrent cardiac myxoma: seeding or multifocal disease? Ann Thorac Surg 1998;66:285-8.